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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/40, 31/19, 9/20 — A1

(11) International Publication Number: **WO 99/49896**

(43) International Publication Date: 7 October 1999 (07.10.99)

(21) International Application Number: PCT/KR99/00157

(22) International Filing Date: 31 March 1999 (31.03.99)

(30) Priority Data:
1998/11172 31 March 1998 (31.03.98) KR

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(81) Designated States: AU, CA, CN, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A DRUG COMPOSITION CONTAINING SODIUM PRAVASTATIN

(57) Abstract

The present invention relates to a drug composition containing sodium pravastatin and more particularly, to the drug composition containing further β–cyclodextrin as stabilizer for sodium pravastatin, thus enhancing the stability of sodium pravastatin which is unstable at high humidity and temperature.

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A DRUG COMPOSITION CONTAINING SODIUM PRAVASTATIN

BACKGROUND OF THE INVENTION

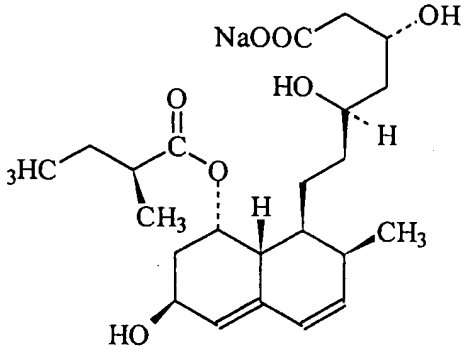
Field of the Invention

The present invention relates to a drug composition containing sodium pravastatin and more particularly, to the drug composition containing further β-cyclodextrin as stabilizer for sodium pravastatin, thus enhancing the stability of sodium pravastatin which is unstable at high humidity and temperature.

Description of the Related Art

Hyperlipidemia is a symptom characterized by high levels of lipids (cholesterol, neutral lipid, phospholipid, free fatty acid, etc.) in the plasma, and is associated with a number of serious disorders, notably arteriosclerosis, hypertension, ischemic heart disease, pancreatitis, etc.

To reduce the blood lipid levels, various drugs have been developed so far. As expressed in the following formula, sodium pravastatin among these drugs is known to be useful in the treatment of hyperlipidemia, since it serves to inhibit the activity of hydroxylmethyl glutaryl CoA reductase, which results in suppressing the synthesis of cholesterol. Sodium pravastatin generates its lactones and several isomers at high humidity and temperature.



For formulating a drug composition containing sodium pravastatin as

active ingredient, the conventional method has adopted its manufacturing process using some commonly available excipients such as lactose, silicon dioxide, sodium cross-camellose, micro-crystallized cellulose and polyvinyl pyrrolidone.

For example, the general drug composition contains sodium pravastatin, lactose, micro-crystallized cellulose, polyvinyl pyrrolidone, sodium cross-camellose and magnesium stearate (VIDAL, p.568(1997), ELISOR; VIDAL, pp.1750-1751(1997), VASTEN 20mg; ROTE LISTE 58 038(1996), PRAVASTIN 5mg/10mg/20mg). However, the drug composition consisting of the above excipient is rapidly degraded at high humidity and temperature.

SUMMARY OF THE INVENTION

To overcome the shortcoming that the conventional method has faced with, the inventors have completed this invention with a notion that β-cyclodextrin may encloses molecules with a low-molecular weight which may block any substances at the surrounding environment.

Accordingly, it is an object of this invention to provide a drug composition comprising sodium pravastatin, excipient, binder, lubricants, disintegrator and β-cyclodextrin, whereby enhancing the stability of sodium pravastatin which is unstable at high humidity and temperature.

Description of the Drawings

Fig. 1a is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 40℃.

Fig. 1b is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 50℃.

Fig. 1c is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 60℃.

Fig. 1d is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 70℃.

Fig. 2a is a graph which shows the stability of drug composition prepared according to example 2 and comparative example 2 at 40℃.

Fig. 2b is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 50℃.

Fig. 2c is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 60℃.

Fig. 2d is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 70℃.

Fig. 3a is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 40℃.

Fig. 3b is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 50℃.

Fig. 3c is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 60℃.

Fig. 3d is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 70℃.

Fig. 4a is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 40℃.

Fig. 4b is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 50℃.

Fig. 4c is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 60℃.

Fig. 4d is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 70℃.

Fig. 5a is a graph which shows the stability of drug composition

prepared according to example 5 and comparative example 5 at 40℃.

Fig. 5b is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 at 50℃.

Fig. 5c is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 at 60℃.

Fig. 5d is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 at 70℃.

Fig. 6a is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 under accelerated condition (40℃/75% R.H.) at 40℃.

Fig. 6b is a graph which shows the stability of drug composition prepared according to example 2 and comparative example 2 under accelerated condition (40℃/75% R.H.) at 40℃.

Fig. 6c is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 under accelerated condition (40℃/75% R.H.) at 40℃.

Fig. 6d is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 under accelerated condition (40℃/75% R.H.) at 40℃.

Fig. 6e is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 under accelerated condition (40℃/75% R.H.) at 40℃.

Fig. 7a is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 40℃.

Fig. 7b is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 50℃.

Fig. 7c is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 60℃.

Fig. 7d is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 70℃.

Detailed Description of the Invention

This invention is characterized by a drug composition comprising sodium pravastatin as active ingredient and β-cyclodextrin as stabilizer as well as excipient, binder, disintegrator and lubricant.

This invention is explained in detail as set forth:

This invention pertains to the drug composition containing sodium pravastatin as active ingredient which has better stability in the mechanism that β-cyclodextrin encloses some molecules with a low-molecular weight to block any substances at the surrounding environment, thus preventing the rapid degradation of the drug composition at high temperature and humidity.

The drug composition of this invention comprises the following ingredients: sodium pravastatin as active ingredient; β-cyclodextrin as stabilizer; excipient such as lactose, starch and micro-crystallized cellulose; binder such as hydroxypropyl cellulose, non-crystallized cellulose, hydroxypropyl methyl cellulose and dextrin; disintegrator such as low-substituted hydoxypropyl cellulose and sodium cross-camellose; and lubricant such as magnesium stearate, talc and stearic acid.

The amount of sodium pravastatin as active ingredient, is advantageously in the range of 2 to 50wt% in proportion to the total drug composition, preferably in the range of 2 to 30wt%, at such levels, the drug composition serves to inhibit the activity of hydroxylmethyl glutaryl CoA reductase which results in suppressing the synthesis of cholesterol. If the amount of sodium pravastatin is less than 2wt%, a drug compliance is reduced due to increased weight of tablet; however, in case of exceeding 50wt%, a dose adjustment of each patient becomes difficult.

Since the sodium pravastatin is apt to form its lactones and several kinds of isomers at high humidity and temperature, β-cyclodextrin is added to the drug composition of this invention as a stabilizer so as to prevent such structural transformations. Unlike the conventional method using the common excipients which leads to the rapid degradation of a drug composition, the addition of β-cyclodextrin as a stabilizer according to this invention contributes to production of a drug composition with better stability at high humidity and temperature.

According to this invention, the amount of β-cyclodextrin is advantageously in the range of 50 to 5,000 weight parts in proportion to 100 weight parts of sodium pravastatin, preferably in the range of 100 to 3,000 weight parts. If the amount of β-cyclodextrin is less than 50 weight parts, insufficiently stabilized sodium pravastatin, is degraded at high humidity and temperature; in case of exceeding 5,000 weight parts, the formulation becomes difficult.

In addition to sodium pravastatin as active ingredient and β-cyclodextrin as stabilizer, the drug composition of this invention contains some additives such as excipient, binder, disintegrator and lubricant.

The excipient of this invention is at least one selected from the group consisting of corn starch, potato starch, wheat starch, lactose, white sugar, glucose, fructose, D-mannitol, precipitated calcium carbonate, micro-crystallized cellulose, dextrin and methyl cellulose; it is preferred that the amount of excipient is in the range of 5-90wt% to the total drug composition.

The binder of this invention is at least one selected from the group consisting of gelatin, methyl cellulose, non-crystallized cellulose, hydroxy cellulose, hydroxymethyl cellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, dextrin and polyvinyl alcohol; it is preferred

that the amount of binder is in the range of 2.5-35wt% to the total drug composition.

The disintegrator of this invention is at least one selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl starch, polyvinyl pyrrolidone, ethyl cellulose and low-substituted hydoxypropyl cellulose; it is preferred that the amount of disintegrator is in the range of 0.5-10wt% to the total drug composition.

The lubricant of this invention is at least one selected from the group consisting of stearic acid, magnesium stearate, talc, fluidized paraffin and rigid anhydrous silic acid; it is preferred that the amount of lubricant is in the range of 0.25-5wt% to the total drug composition. Also, some edible dye may be added to the drug composition depending on the objective of this invention.

The drug composition comprising the aforementioned ingredients is prepared as follows:

First, sodium pravastatin and β-cyclodextrin are ground in an appropriate container for tens of minutes, followed by the addition of one or more excipients. Then, for the purpose of use, the mixture is under wet granulation in the presence of a solution containing one or more binders and solvent (water, isopropanol, dichloromethane, etc.) and dried. As an alternative procedure, one or more lubricants and/or binders are added to the mixture of sodium pravastatin and β-cyclodextrin and under drying granulation using a rolling compactor.

After the procedure is completed, the drug composition of this invention is prepared with the addition of one or more disintegrators, lubricants or binders, if deemed necessary.

As such, the drug composition of this invention prepared as mentioned above, comprising sodium pravastatin as an active ingredient and β-cyclodextrin as stabilizer is mixed with some pharmaceutically acceptable

carriers to formulate a variety of dosage forms (e.g., tablet, capsule, powder, granule and pill) in the pharmaceutical field.

The examples of the carriers according to this invention include some pharmaceutically applicable carrier such as binder, lubricant, disintegrator, excipient, stabilizer and conspergative agent.

Further, to prevent the degradation of the drug composition by gastric acid during oral administration, the concurrent use of an antacid and enteric coated tablet and granule are recommended. It is recommended that the drug composition of this invention be orally administered as a desirable route (ABPI Compendium of Data Sheets, VIDAL, ROTE LISTE, Physicians' Desk Reference).

According to this invention, a dose of the active ingredient varies depending on its absorption rate, inactivation rate and excretion rate, and other variations such as age, sex and conditions of patients, severity of disease, etc. The regimen of the drug composition is recommended as follows: a) the usual dose of the drug composition for adult is 10-40mg per day before bedtime with initial dose of 10-20mg once daily (ABPI Compendium of Data Sheets, pp.1780-1782(1995-1996), LIPOSTAT TABLETS). The usual dose for adult is 10-40mg and in the case of the elderly patients, the usual dose is given at the dose of less than 20mg (Physicians' Desk Reference, pp.732-735(1995), PRAVACHOL). Further, another initial dose is 10mg once per day with a maximum dose of 40mg in the evening (VIDAL, p.568(1997), ELISOR; pp.1750-1751(1997) VASTEN), while the initial dose is 5-10mg once daily with a maximum dose of 40mg (ROTE LISTE, 58 038(1996), PRAVASIN 5mg/10mg/20mg).

Based on the cited references, therefore, it is preferred that the drug composition of this invention is administered at a dose of 5-40mg once daily in the evening or before bedtime.

As described above, some physical strength is given to the drug

composition comprising sodium pravastatin as active ingredient and β-cyclodextrin as stabilizer, so formulated, for enclosing the active ingredient. As a result, the drug composition containing β-cyclodextrin shows excellent stability at high temperature and humidity (Fig. 1a-7d).

When the drug composition of this invention is compared with comparative examples and A tablet without β-cyclodextrin as shown in Fig. 1a-5d and Fig. 7a-7d, it is evident that the drug composition of this invention has much better stability on the temperature than that of the conventional drug composition. Also, for stability on humidity, the same results were revealed in Fig. 6a-6e. Furthermore, the process for preparing the drug composition of this invention may utilize the existing machine such as a rolling compactor in mass-production, thereby improving the aspects of economics such as the additional cost for production.

The following specific examples are intended to be illustrative of the invention and should not be construed as limiting the scope of the invention as defined by appended claims.

Example 1

Sodium pravastatin	5mg
β-cyclodextrin	120.09mg
Hydroxypropyl cellulose	5mg
Low-substituted hydroxypropyl cellulose	13.5mg
Lactose	48.51mg
Magnesium stearate	0.9mg

A mixture of sodium pravastatin and β-cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose, the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl cellulose solution). The solution was dried in an oven at 30-

40℃ and sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Example 2

Sodium pravastatin	5mg
β-cyclodextrin	127.09mg
Hydroxypropyl cellulose	5mg
Low-substituted hydroxypropyl cellulose	13.5mg
Lactose	30.0mg
Corn starch	18.51mg
Magnesium stearate	0.9mg

A mixture of sodium pravastatin and β-cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose and corn starch, the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl cellulose solution). The solution was dried in an oven at 30-40℃ and sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Example 3

Ssodium pravastatin	5mg
β-cyclodextrin	127.09mg
Rigid anhydrous silicic acid	1.75mg
Low-substituted hydroxypropyl cellulose	10.0mg
Lactose	30.0mg
Magnesium stearate	1.6mg

A mixture of sodium pravastatin and β-cyclodextrin was ground in a

reactor for 20 mins. With the addition of lactose, rigid anhydrous silicic acid and magnesium stearate (0.8mg), the reacting solution was well mixed and subjected to rolling compactor, finally preparing dried granules. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Example 4

Sodium pravastatin	5mg
β-cyclodextrin	127.09mg
Low-substituted hydroxypropyl cellulose	10.0mg
Lactose	20.07mg
Corn starch	28.0mg
Dextrin	7.8mg
Red-dye # 3	0.12mg
Blue-dye #1 aluminium lake	0.12mg
Magnesium stearate	1.6mg

A mixture of sodium pravastatin and β-cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose and corn starch (14.0mg), the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (dextrin) containing dyes (red-dye # 3 and blue-dye #1 aluminium lake), followed by drying in oven at 30-40℃. With the addition of remaining corn starch (14.0mg), low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Example 5

Sodium pravastatin	5mg
β-cyclodextrin	127.09mg
Lactose	30.31mg

Potato starch	30.0mg
Polyvinyl alcohol	7.8mg
Magnesium stearate	1.6mg

A mixture of sodium pravastatin and β-cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose and potato starch, the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (polyvinyl alcohol), followed by drying in oven at 30-40℃. With the addition of magnesium stearate, the mixture was well mixed for its tableting process.

Comparative example 1

Sodium pravastatin	5mg
Hydroxypropyl cellulose	127.09mg
Low-substituted hydroxypropyl cellulose	10.0mg
Lactose	175.6mg
Magnesium stearate	0.9mg

A mixture of sodium pravastatin and lactose was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl cellulose), followed by drying in oven at 30-40℃. Then, the dried preparation was sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Comparative example 2

Sodium pravastatin	5mg
Hydroxypropyl cellulose	5mg
Low-substituted hydroxypropyl cellulose	13.5mg

Lactose	157.09mg
Corn starch	18.51mg
Magnesium stearate	0.9mg

A mixture of sodium pravastatin, lactose and corn starch was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl cellulose), followed by drying in oven at 30-40℃. Then, the dried preparation was sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Comparative example 3

Sodium pravastatin	5mg
Rigid anhydrous silicic acid	1.75mg
Low-substituted hydroxypropyl cellulose	10.0mg
Lactose	181.65mg
Magnesium stearate	1.6mg

With the addition of sodium pravastatin, rigid anhydrous silicic acid and magnesium stearate (0.8mg), the reacting solution was well mixed and subjected to rolling compactor, finally preparing dried granules. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate (0.8mg), the mixture was well mixed for its tableting process.

Comparative example 4

Sodium pravastatin	5mg
Low-substituted hydroxypropyl cellulose	10.0mg
Lactose	120.27mg
Corn starch	55.09mg
Dextrin	7.8mg

Red-dye # 3	0.12mg
Blue-dye #1 alluminium lake	0.12mg
Magnesium stearate	1.6mg

With the addition of sodium pravastatin, lactose and corn starch (half of the content), the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (dextrin) containing dyes (red-dye # 3 and blue-dye #1 aluminium lake), followed by drying in oven at 30-40℃. With the addition of remaining corn starch, low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Comparative example 5

Sodium pravastatin	5mg
Lactose	130.31mg
Potato starch	57.09mg
Polyvinyl alcohol	5.7mg
Magnesium stearate	1.9mg

With the addition of sodium pravastatin, lactose and potato starch, the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (polyvinyl alcohol), followed by drying in oven at 30-40℃. With the addition of magnesium stearate, the mixture was well mixed for its tableting process.

Test 1

In order to confirm the effect of this invention, final preparations were tested under rigorous temperature condition (40, 50, 60 and 70℃) with regard to an alteration of content and degraded products by using the following machine, and the results are shown in Table 1a-1e and Fig. 1a-5d:

1) High performance liquid chromatography : Waters 510

Detector: ultraviolet absorption spectrophotometer (238nm)

Column: Cosmosil C_{18}

Mobile phase: methanol · H2O · TEA · acetic acid (500:500:1:1)

Flow rate: 1.5ml/min

Injection amount: 5 $\mu\ell$

2) Autosampler: Waters 717

3) Integrator: Waters 740

4) Detector: Waters 486

5) Oven

SY-IN.G (SUN YOUNG Co., Korea), if treated at 40℃

VO-C-2 (Space Science Co., Korea), if treated at 50℃ and 60℃

NDO-600-ND (EYELA Co., Korea), if treated at 70℃

6) Life tester : JEIO TECH. Co. Ltd., TH-10

Table 1a

Category		At start	After 7 days	After 15 days	After 23 days	After 29 days
Exam. 1 (remainder, %)*	40℃	100	99.8	99.3	98.9	98.0
	50℃	100	97.9	97.8	96.4	95.6
	60℃	100	99.5	97.8	91.3	90.0
	70℃	100	97.4	89.8	84.1	80.1
Comp. Exam. 1 (remainder, %)*	40℃	100	99.1	97.9	95.4	93.1
	50℃	100	93.7	92.0	91.9	89.0
	60℃	100	93.3	92.3	86.5	83.2
	70℃	100	91.5	78.8	67.5	64.8

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1b

Category		At start	After 7 days	After 15 days	After 23 days	After 29 days
Exam. 2 (remainder, %)*	40℃	100	99.7	99.0	98.7	98.6
	50℃	100	98.9	97.5	96.0	95.3
	60℃	100	98.8	97.3	92.0	89.9
	70℃	100	97.0	88.5	83.9	79.2
Comp. Exam. 2 (remainder, %)*	40℃	100	99.0	97.5	95.2	94.0
	50℃	100	92.8	91.5	91.0	89.2
	60℃	100	91.2	90.6	88.5	82.5
	70℃	100	90.9	80.3	72.0	63.9

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1c

Category		At start	After 7 days	After 15 days	After 23 days	After 29 days
Exam. 3 (remainder, %)*	40℃	100	99.9	99.5	99.0	98.6
	50℃	100	98.2	97.8	97.0	96.0
	60℃	100	98.2	97.0	93.5	90.2
	70℃	100	96.2	89.6	82.0	75.3
Comp. Exam. 3 (remainder, %)*	40℃	100	99.2	98.1	96.7	95.5
	50℃	100	93.5	92.9	92.1	90.8
	60℃	100	91.3	90.2	89.3	80.5
	70℃	100	89.6	79.6	70.3	65.0

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1d

Category		At start	After 7 days	After 15 days	After 23 days	After 29 days
Exam. 4 (remainder, %)*	40℃	100	99.2	98.8	96.5	96.0
	50℃	100	98.6	97.7	95.8	95.2
	60℃	100	98.0	96.8	92.6	88.8
	70℃	100	96.0	88.2	80.2	79.6
Comp. Exam. 4 (remainder, %)*	40℃	100	99.0	98.0	95.0	94.5
	50℃	100	92.3	91.5	90.2	89.6
	60℃	100	90.6	89.9	86.0	80.0
	70℃	100	88.5	80.3	68.8	60.2

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1e

Category		At start	After 7 days	After 15 days	After 23 days	After 29 days
Exam. 5 (remainder, %)*	40℃	100	99.7	99.0	99.0	98.5
	50℃	100	98.9	97.0	97.2	95.2
	60℃	100	98.5	97.5	93.3	89.9
	70℃	100	96.5	88.8	83.2	80.2
Comp. Exam. 5 (remainder, %)*	40℃	100	99.0	98.0	96.8	94.5
	50℃	100	94.0	93.2	92.8	90.0
	60℃	100	93.0	92.6	89.2	80.0
	70℃	100	90.5	80.9	75.5	70.0

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Test 2

In order to confirm the effect of this invention, final preparations were tested under accelerated condition (40℃/75%R.H.) with regard to an alteration of content and decomposed products, and the results are shown in Table 2 and Fig. 6a-6e:

Table 2

Category		At start	After 1 month	After 2 months	After 3 months
Remainder* (%)	Exam. 1	100	97.5	93.1	90.0
	Exam. 2	100	97.8	92.9	90.3
	Exam. 3	100	98.0	92.5	89.1
	Exam. 4	100	95.0	90.1	87.1
	Exam. 5	100	96.6	93.5	89.0
	Com. Exam. 1	100	92.0	89.5	84.4
	Com. Exam. 2	100	92.5	88.5	83.1
	Com. Exam. 3	100	93.1	88.0	82.3
	Com. Exam. 4	100	94.0	86.9	80.0
	Com. Exam. 5	100	91.3	89.3	83.0

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Test 3

In order to confirm the effect of this invention, final preparation (prepared in example 1) and A tablet™ (commercial product, Korea) were tested under rigorous temperature condition (40, 50, 60 and 70℃) with regard to an alteration of content and decomposed products, and the results are shown in Table 3 and Fig. 7a-7d:

Table 3

Category		At start	After 7 days	After 15 days	After 23 days	After 29 days
Exam. 1 (remainder, %)*	40℃	100	99.8	99.3	98.9	98.0
	50℃	100	97.9	97.8	96.4	95.6
	60℃	100	99.5	97.8	91.3	90.0
	70℃	100	97.4	89.8	84.1	80.1
A Tablet™ (remainder, %)*	40℃	100	99.4	99.0	98.6	97.5
	50℃	100	98.0	96.9	93.6	90.1
	60℃	100	98.5	95.1	89.2	87.5
	70℃	100	89.1	84.3	76.8	65.9

* the remaining amount of sodium pravastatin among the pharmaceutical composition

As discussed above, the pharmaceutical composition of this invention, comprising sodium pravastatin as active ingredient and β-cyclodextrin as stabilizer, has excellent stability at high humidity and temperature so that it prohibits the sodium pravastatin from decomposing rapidly, and may employ the existing machine in mass production, thereby improving the aspects of economics such as the additional cost for production.

CLAIMS

What is claimed is:

1. A drug composition comprising sodium pravastatin as active ingredient, excipient, binder, disintegrator and lubricants, characterized in that the composition contains β-cyclodextrin as stabilizer for the sodium pravastatin.

2. The drug composition according to claim 1, wherein the amount of sodium pravastatin is in the range of 2-50wt% to the total drug composition.

3. The drug composition according to claim 1, wherein the amount of β-cyclodextrin is 50-5,000 weight part to 100 weight part of the sodium pravastatin.

4. The drug composition according to claim 1, wherein the amount of excipient is in the range of 5-90wt% to the total drug composition.

5. The drug composition according to claim 1 or 4, wherein the excipient is at least one selected from the group consisting of corn starch, potato starch, wheat starch, lactose, white sugar, glucose, fructose, D-mannitol, precipitated calcium carbonate, micro-crystallized cellulose, dextrin and methyl cellulose.

6. The drug composition according to claim 1, wherein the amount of binder is in the range of 2.5-35wt% to the total drug composition.

7. The drug composition according to claim 1 or 6, wherein the binder is at least one selected from the group consisting of gelatin, methyl cellulose, non-crystallized cellulose, hydroxy cellulose, hydroxymethyl cellulose, glycerin,

hydroxypropyl cellulose, hydroxypropyl methyl cellulose, dextrin and polyvinyl alcohol.

8. The drug composition according to claim 1, wherein the amount of disintegrator is in the range of 0.5-10wt% to the total drug composition.

9. The drug composition according to claim 1 or 8, wherein the disintegrator is at least one selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl starch, polyvinyl pyrrolidone, ethyl cellulose and low-substituted hydoxypropyl cellulose.

10. The drug composition according to claim 1, wherein the amount of lubricants is in the range of 0.25-5wt% to the total drug composition.

11. The drug composition according to claim 1 or 10, wherein the lubricants is at least one selected from the group consisting of stearic acid, magnesium stearate, talc, fluidized paraffin and rigid anhydrous silic acid.

FIGURE

Fig. 1a

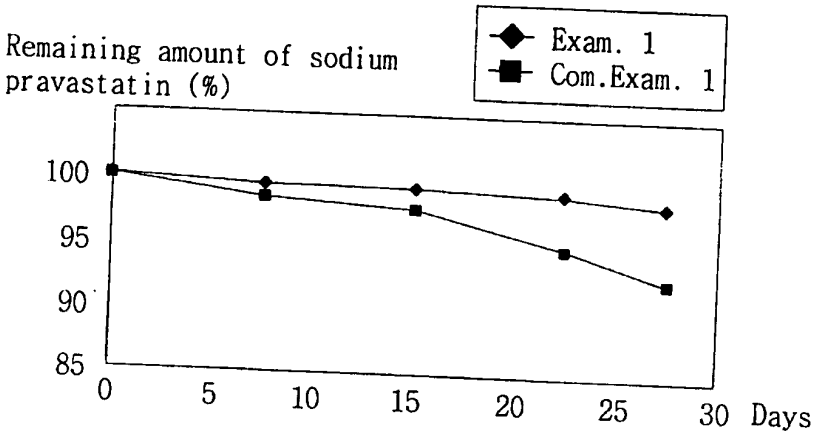


Fig. 1b

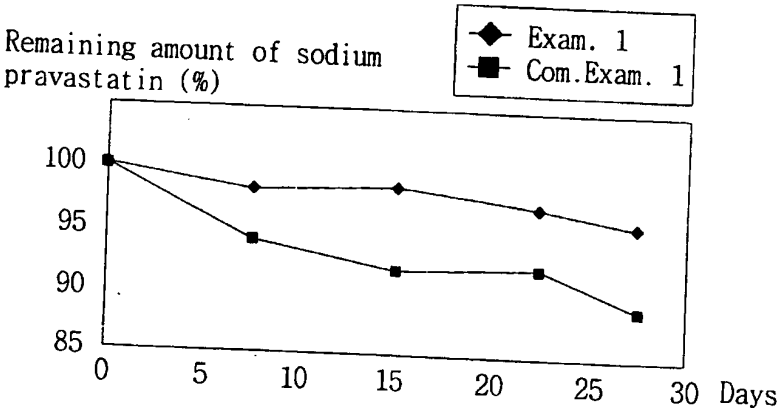


Fig. 1c

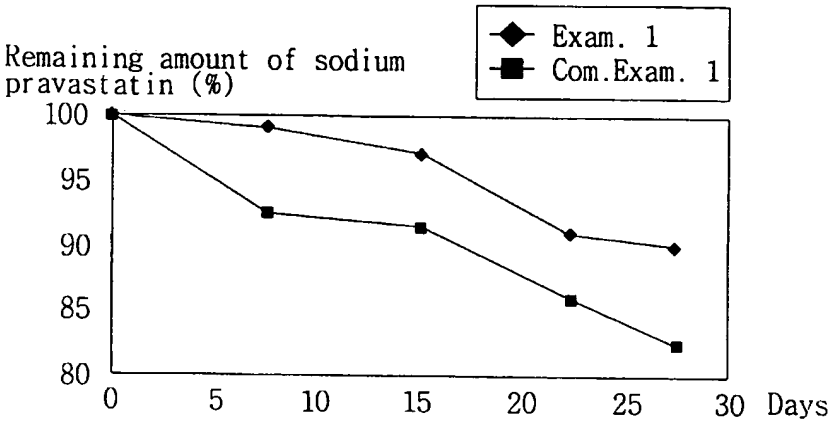

Remaining amount of sodium pravastatin (%)
Exam. 1
Com.Exam. 1
100
95
90
85
80
0
5
10
15
20
25
30
Days

Fig. 1d

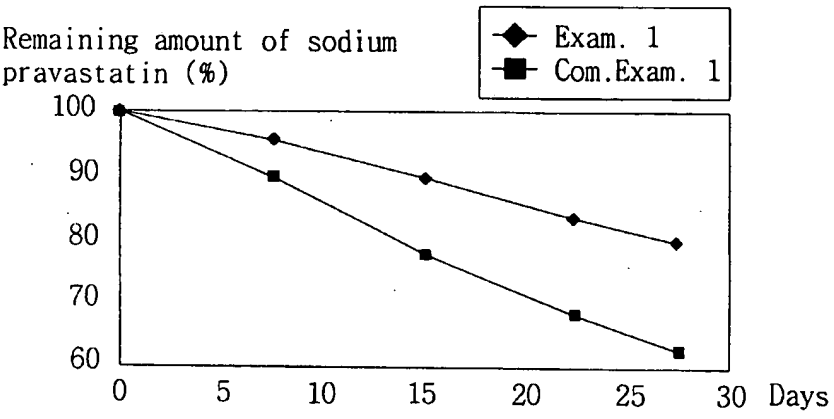

Remaining amount of sodium pravastatin (%)
Exam. 1
Com.Exam. 1
100
90
80
70
60
0
5
10
15
20
25
30
Days

Fig. 2a

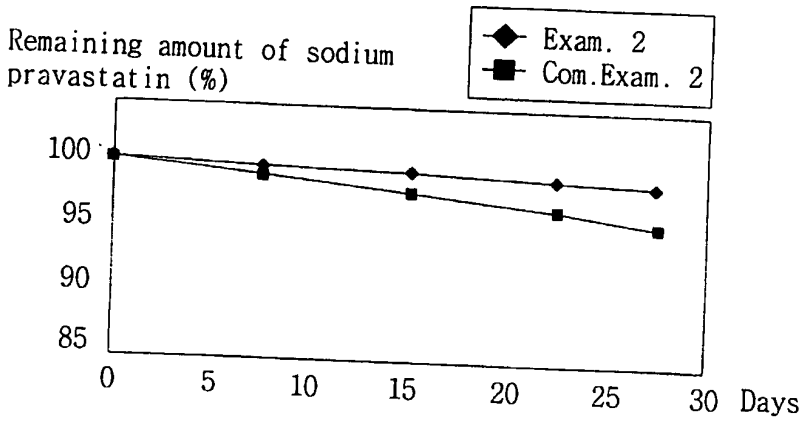

Remaining amount of sodium pravastatin (%)
Exam. 2
Com.Exam. 2
100
95
90
85
0
5
10
15
20
25
30
Days

Fig. 2b

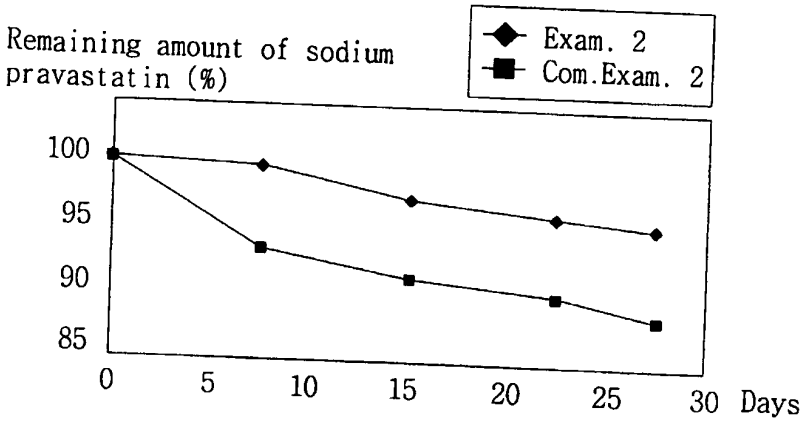

Remaining amount of sodium pravastatin (%)
Exam. 2
Com.Exam. 2
100
95
90
85
0
5
10
15
20
25
30
Days

Fig. 2c

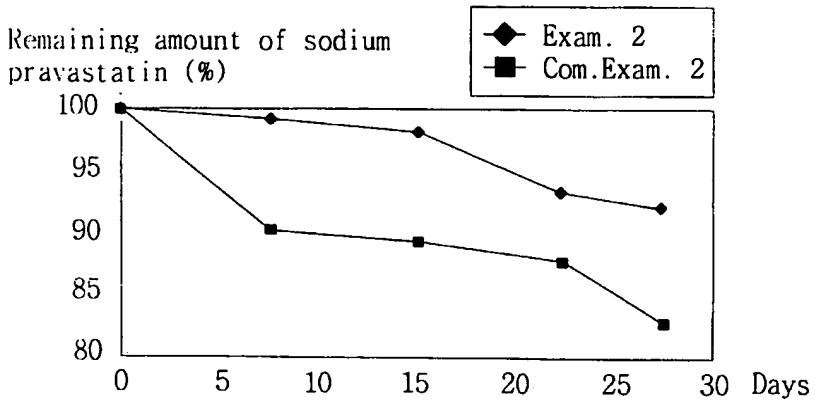

Remaining amount of sodium pravastatin (%)
Exam. 2
Com.Exam. 2
100
95
90
85
80
0
5
10
15
20
25
30
Days

Fig. 2d

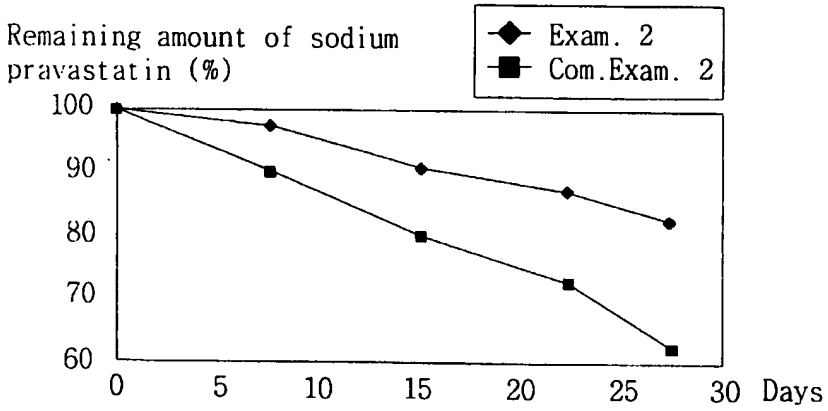

Remaining amount of sodium pravastatin (%)
Exam. 2
Com.Exam. 2
100
90
80
70
60
0
5
10
15
20
25
30
Days

Fig. 3a

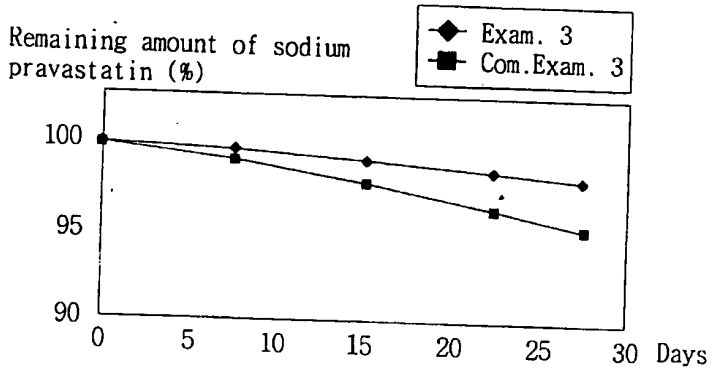

Remaining amount of sodium pravastatin (%)
Exam. 3
Com.Exam. 3
100
95
90
0
5
10
15
20
25
30
Days

Fig. 3b

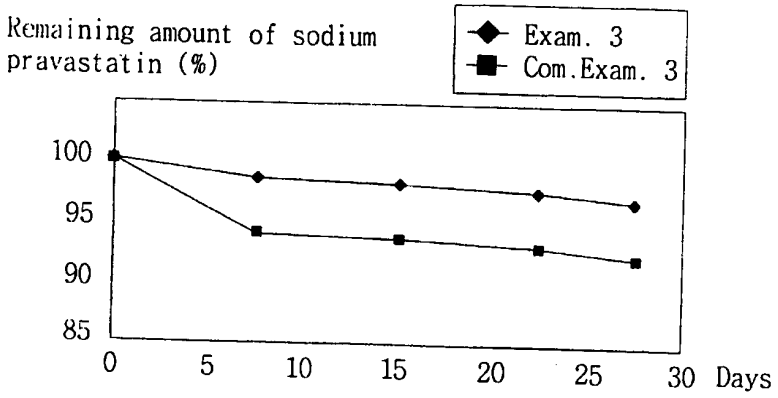

Remaining amount of sodium pravastatin (%)
Exam. 3
Com.Exam. 3
100
95
90
85
0
5
10
15
20
25
30
Days

Fig. 3c

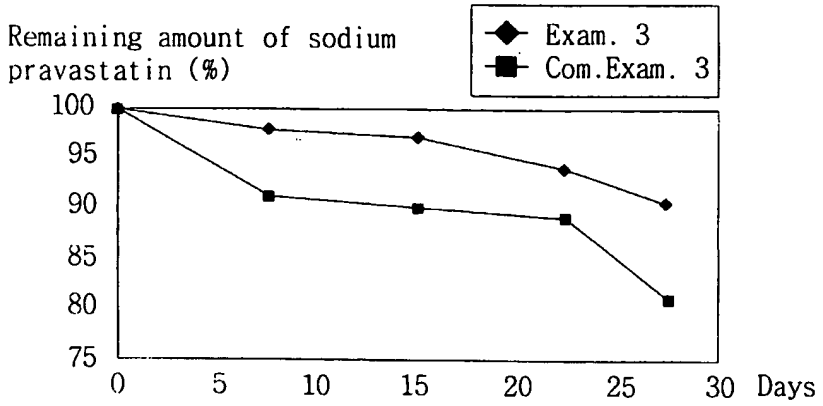

Remaining amount of sodium pravastatin (%)
Exam. 3
Com.Exam. 3
100
95
90
85
80
75
0
5
10
15
20
25
30
Days

Fig. 3d

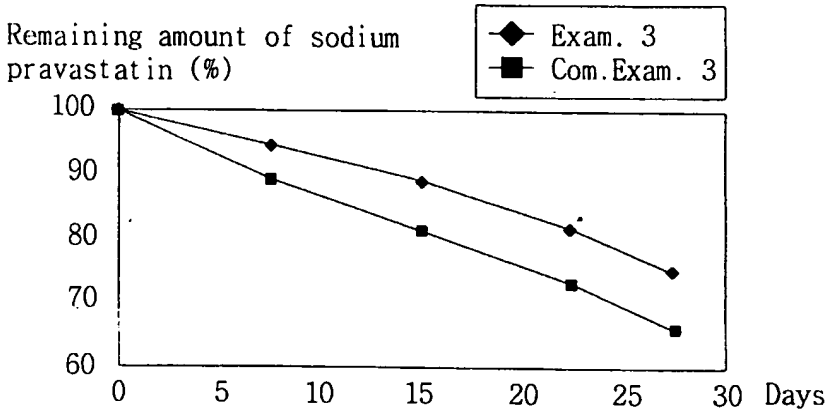

Remaining amount of sodium pravastatin (%)
Exam. 3
Com.Exam. 3
100
90
80
70
60
0
5
10
15
20
25
30
Days

Fig. 4a

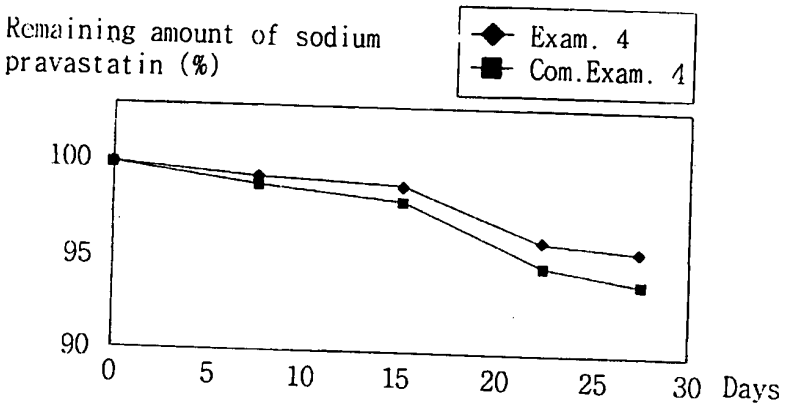

Remaining amount of sodium pravastatin (%)
Exam. 4
Com.Exam. 4
100
95
90
0
5
10
15
20
25
30
Days

Fig. 4b

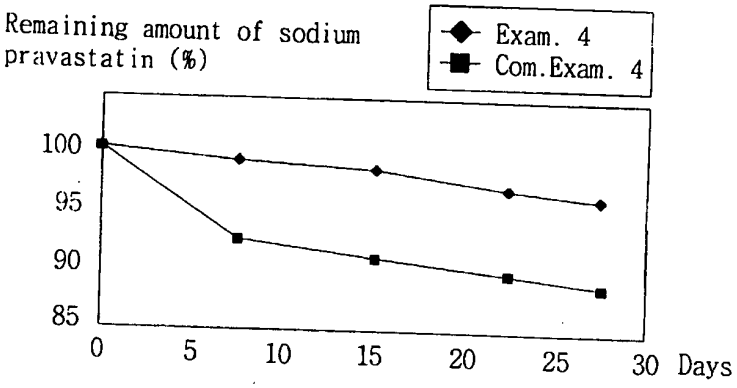

Remaining amount of sodium pravastatin (%)
Exam. 4
Com.Exam. 4
100
95
90
85
0
5
10
15
20
25
30
Days

Fig. 4c

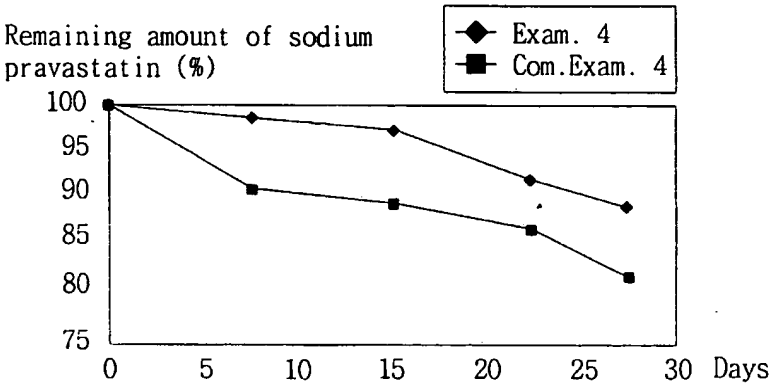

Remaining amount of sodium pravastatin (%)
Exam. 4
Com.Exam. 4
100
95
90
85
80
75
0
5
10
15
20
25
30
Days

Fig. 4d

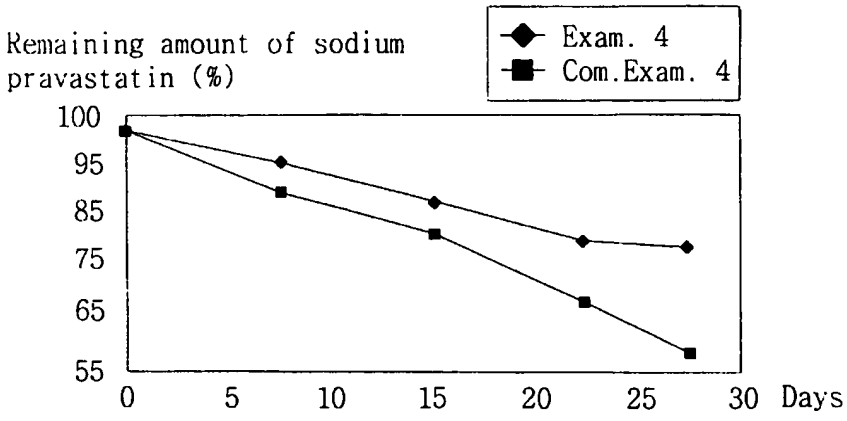

Remaining amount of sodium pravastatin (%)
Exam. 4
Com.Exam. 4
100
95
85
75
65
55
0
5
10
15
20
25
30
Days

Fig. 5a

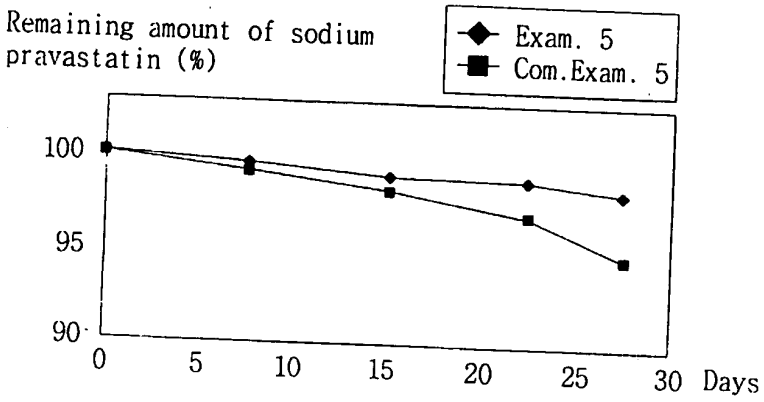

Remaining amount of sodium pravastatin (%)
Exam. 5
Com.Exam. 5
100
95
90
0
5
10
15
20
25
30
Days

Fig. 5b

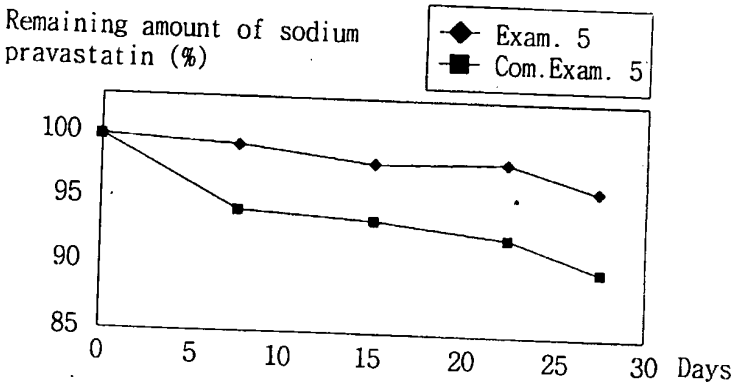

Remaining amount of sodium pravastatin (%)
Exam. 5
Com.Exam. 5
100
95
90
85
0
5
10
15
20
25
30
Days

Fig. 5c

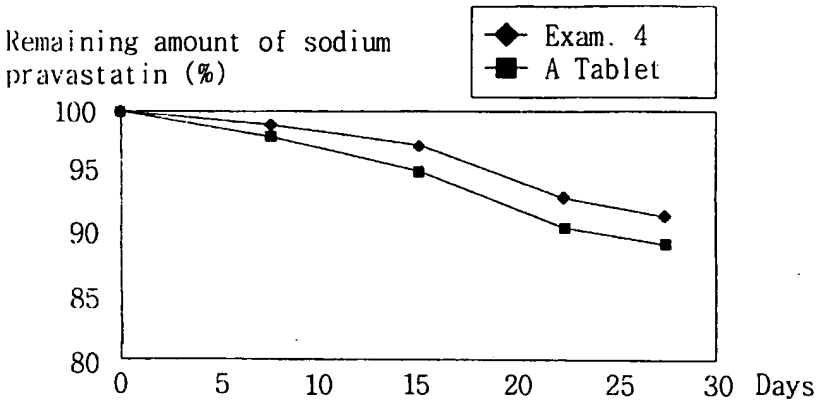

Remaining amount of sodium pravastatin (%)
Exam. 4
A Tablet
100
95
90
85
80
0
5
10
15
20
25
30
Days

Fig. 5d

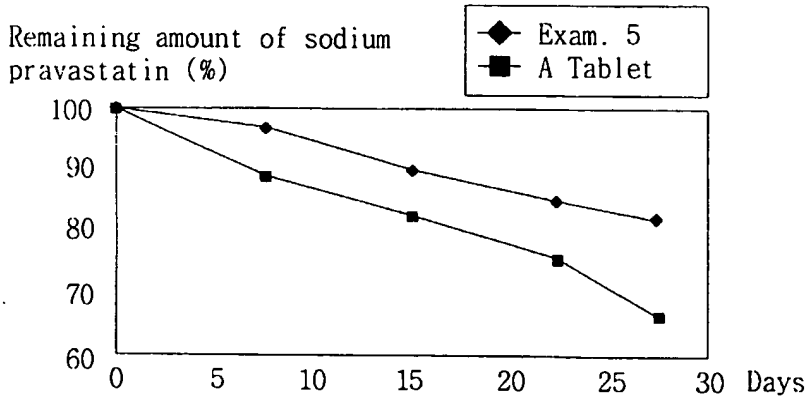

Remaining amount of sodium pravastatin (%)
Exam. 5
A Tablet
100
90
80
70
60
0
5
10
15
20
25
30
Days

Fig. 6a

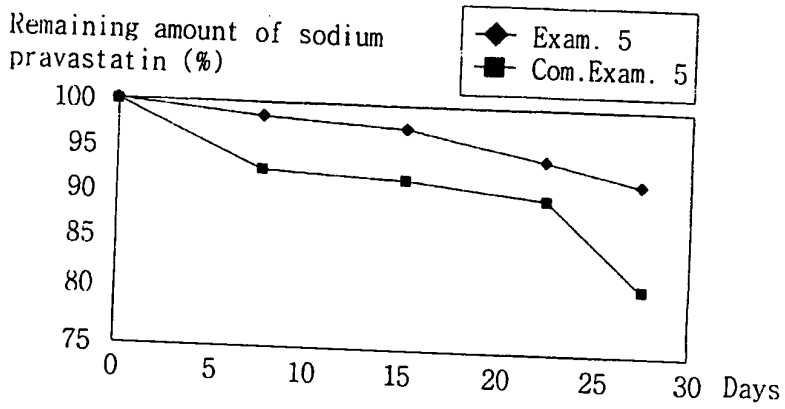

Remaining amount of sodium pravastatin (%)
Exam. 5
Com.Exam. 5
100
95
90
85
80
75
0
5
10
15
20
25
30
Days

Fig. 6b

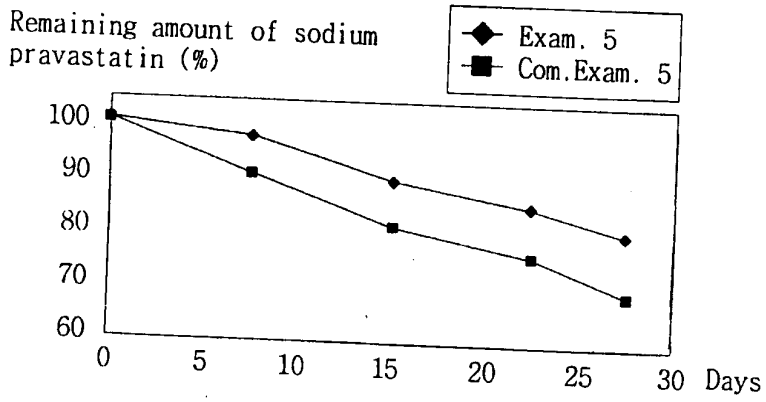

Remaining amount of sodium pravastatin (%)
Exam. 5
Com.Exam. 5
100
90
80
70
60
0
5
10
15
20
25
30
Days

Fig. 6c

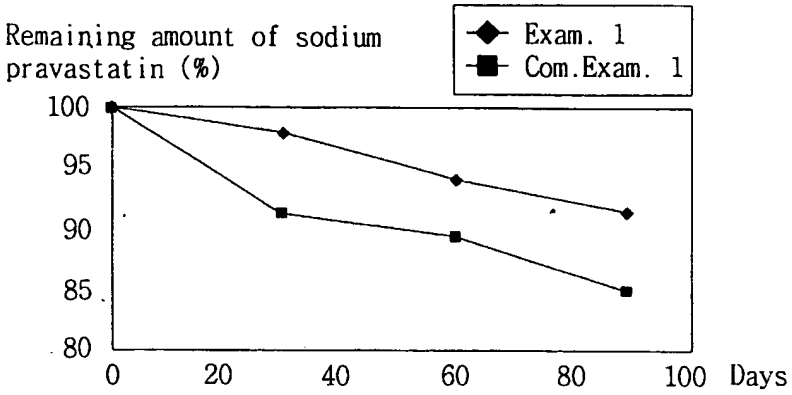

Remaining amount of sodium pravastatin (%)
Exam. 1
Com.Exam. 1
100
95
90
85
80
0
20
40
60
80
100
Days

Fig. 6d

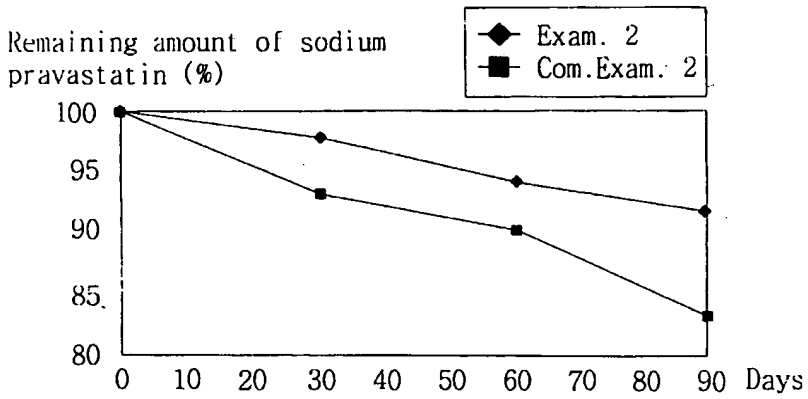

Remaining amount of sodium pravastatin (%)
Exam. 2
Com.Exam. 2
100
95
90
85
80
0
10
20
30
40
50
60
70
80
90
Days

Fig. 6e

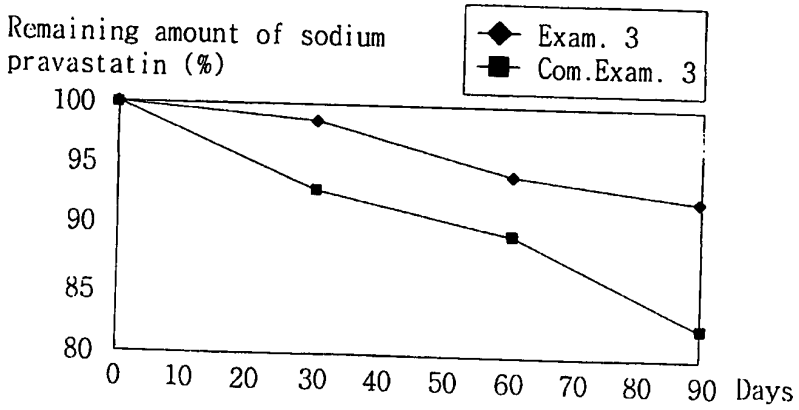

Remaining amount of sodium pravastatin (%)
Exam. 3
Com.Exam. 3
100
95
90
85
80
0 10 20 30 40 50 60 70 80 90 Days

Fig. 7a

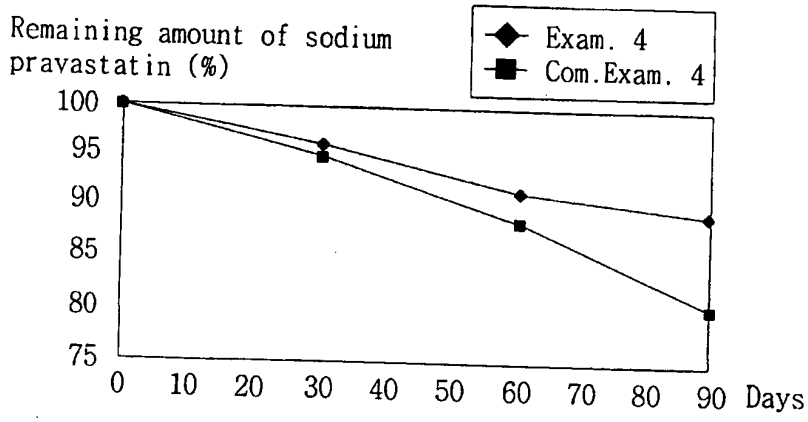

Remaining amount of sodium pravastatin (%)
Exam. 4
Com.Exam. 4
100
95
90
85
80
75
0 10 20 30 40 50 60 70 80 90 Days

Fig. 7b

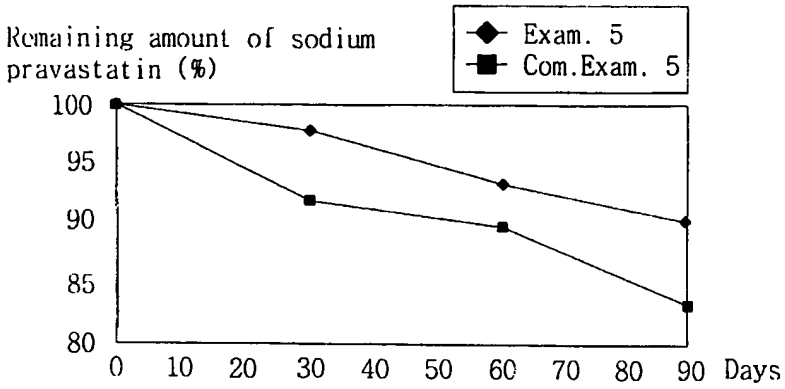

Remaining amount of sodium pravastatin (%)
Exam. 5
Com.Exam. 5
100
95
90
85
80
0 10 20 30 40 50 60 70 80 90 Days

Fig. 7c

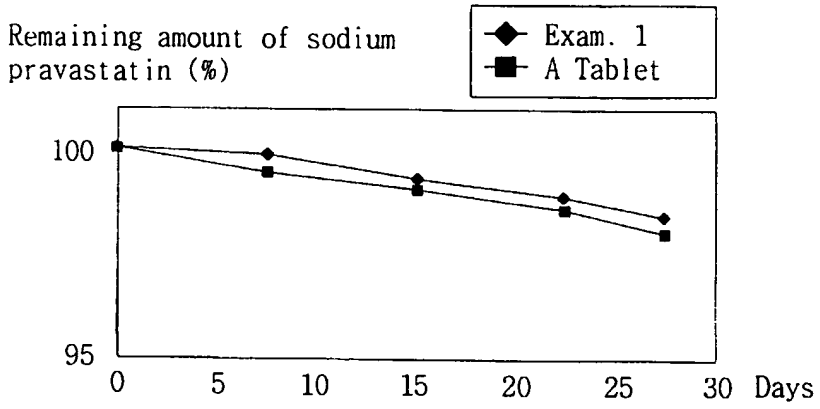
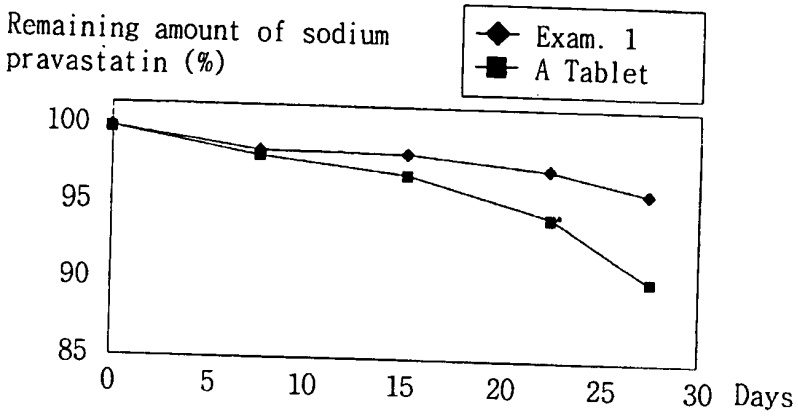

Remaining amount of sodium pravastatin (%)
Exam. 1
A Tablet
100
95
0 5 10 15 20 25 30 Days

Fig. 7d


Remaining amount of sodium pravastatin (%)
Exam. 1
A Tablet
100
95
90
85
0
5
10
15
20
25
30
Days

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00157

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 61 K 47/40, 31/19, 9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 61 K 47/40, 31/19, 9/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 336 298 A1 (E. R. SQIBB & SONS, INC.) 11 October 1989 (11.10.89), totality.	1, 2, 4 - 11
A	DD 232 198 A1 (VEB JENAPHARM) 22 January 1986 (22.01.86), claim; examples 1 - 3.	1, 5, 11
A	DE 32 23 232 A1 (KUREHA KAGAKU KOGYO K.K.) 03 February 1983 (03.02.83), claims 1 - 5.	1, 2

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
28 June 1999 (28.06.99)	27.July 1999 (27.07.99)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Mosser Telephone No. 1/53424/437

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

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